REMARKS

Claims

Claims 1-22 were pending in the instant application. Claims 6, 7, 9, 14 and 16-19 were examined. Claims 1-22 were canceled, and claims 23-27 were added.

The newly added claims do not add or constitute new matter. Support for the newly added claims may be found throughout the specification. Specifically, support for the transgenic mouse recited in claims 23-24 can be found, for example, at page 32, line 26 through page 4, line 5, at page 9, line 24 through page 16, line 11, at page 52, lines 7-19 and at page 53, line 29 through page 54, line 9, of the specification. Support for the method of identifying agents recited in claim 25 can be found, for example, at page 4, lines 6-22 and page 18, line 2 through page 21, line 13, of the specification. Finally, support for the method of producing the transgenic mouse can be found, for example, at page 15, line 17 through page 16, line 11 and at page 52, lines 7-19, of the specification. As such, no new matter has been added by this amendment.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Applicants respectfully request reconsideration of the application in view of the amendments to the claims, and remarks made herein.

Drawings

The Examiner has required new corrected drawings in this application because Figure 5 is illegible. Applicants have submitted herewith a replacement Figure 5. No substantive changes have been made to the information provided in Figure 5. Replacement Figure 5 merely clears up illegible or fuzzy objects contained therein, and is supported by the originally filed specification and figures. Therefore, no new matter has been added. It is believed that the replacement of Figure 5 satisfies the requirement for corrected drawings.

Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 6-7, 9, 14 and 16-19 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a

well-established utility. Applicants respectfully traverse the rejection. Claims 6-7, 9, 14 and 16-19 have been canceled. Applicants submit that the rejection has been overcome as it applies to claims 23-27 in light of the arguments below.

Specifically, the Examiner has stated that the asserted utility for the claimed transgenic mice does not appear to be specific and substantial. The Examiner has based the rejection on the evidence of record allegedly not providing a correlation between the phenotype exhibited by the claimed mice (increased pain threshold) and any disease or disorder. Applicants respectfully disagree. However, although Applicants submit that such a correlation does exist, and is well-established in the art, Applicants do not believe that such a correlation is a requirement to establish utility or for the patentability of the claimed transgenic mouse. Applicants submit that the Examiner's rejection of the claims for lack of utility is improper.

Claims 23-27 and are drawn to a transgenic mouse whose genome comprises a disruption in the TRP6 gene, wherein the mouse exhibits increased pain threshold, and to a method of making said transgenic mouse and a method of using said transgenic mouse. Applicants have asserted in the specification several potential uses for the transgenic knockout mouse, and such uses of transgenic knockout mice are accepted within the art. See, for example, page 4, lines 6-22, page 19, lines 2-10, and page 19, line 18 through page 20, line-21 of the specification. The potential uses specifically relate to using the mice to discover, examine and/or develop potential treatments, which may include therapeutic agents, capable of modulating the phenotype exhibited by the mice, and in particular, capable of modulating or ameliorating the abnormal pain sensitivity exhibited by the mice. Although Applicants have suggested these potential uses for the transgenic mice, many well-established uses for the mice would be recognized by a person skilled in the art.

Applicants submit that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicants submit that the instant specification satisfies these requirements.

The instant specification has demonstrated that disruption of the TRP6 sequence as described in SEQ ID NO:1 in a mouse results in a phenotype specific to that mouse. In particular, the transgenic mice whose genomes comprise this disruption exhibit increased pain threshold, or decreased pain sensitivity, when compared to wild-type mice, which was characterized by an increased latency or time to respond to a thermal stimulus in the hot plate test (See pages 53-54 of

the specification, and Figure 5). The phenotypic parameters of the transgenic mice were evaluated in controlled studies using the hot plate test, which is accepted by the skilled artisan as an indicator of pain response or threshold.

It is generally accepted in the art that transgenic knockout mice, such as those described in the instant application, represent a valuable tool for determining the function of genes in various conditions or disorders. It is also generally accepted that gene function in the mouse is related to and representative of that of human, in light of the homology between the mouse and human genomes. This is why knockout mice represent such a valuable tool. In the present case, the transgenic mouse described in the instant specification would be accepted by the skilled artisan as a model for the role and function of the TRP6 gene in pain pathways. Applicants' disclosure related to the phenotype of the transgenic mice has established that this gene plays a role in pain sensitivity, as noted above. The claimed transgenic mice represent an *in vivo* model of antagonism of the TRP6 gene, which resulted in an increase in pain threshold, or a decrease in pain sensitivity. The value of such an *in vivo* model of TRP6 gene function would be immediately recognized by the skilled artisan. This is supported by the trend to produce such transgenic mice with disruptions in virtually every gene.

The Examiner has stated that no correlation has been established between the increased pain threshold phenotype and any disease or disorder. As noted above, Applicants do not believe that this is a requirement in order to establish that the transgenic mice have utility. It is clearly desirable in the art to modulate or ameliorate pain, and use of an *in vivo* model such as the claimed transgenic mouse would be considered valuable in the process of discovering therapeutic agents for modulating, ameliorating or preventing pain. Applicants also submit that the skilled artisan would recognize that the claimed transgenic mice could be used as a tool for investigating methods for increasing pain threshold or modulating pain sensitivity. As such, the claimed mice clearly have well-established, real world uses that would be evident to the skilled artisan.

The Examiner has cited Crabbe (*Science*, 1999, Vol. 284, pp 1670-1672) as establishing that results obtained from behavioral studies are greatly influenced by the genetic background of the tested mouse. However, the Crabbe reference fails to establish that phenotypic differences between a transgenic knockout mouse and a wild-type control mouse, such as those described in the instant specification, are not real and a result of the disruption of the target gene. In particular, the Crabbe reference describes only one null mutant strain (for the 5-HT1B gene) in comparison to

inbred wild-type strains, and is not representative of a comparison of all mutant knockout mice and their wild-type control counterparts. Further, the number of mice tested was low, and, according to the reference, "made formal statistical assessment of reliability infeasible" (see page 1671, column 3, first full paragraph). The Crabbe reference also states that the results obtained in their study can be interpreted in different ways.

Applicants further contend that the Crabbe reference should not be broadly interpreted to apply to all behavioral studies in mice. This is because Crabbe relates to inconsistencies observed in the open field test, the elevated plus maze, and the water maze test, and fails to describe all behavioral tests. More particularly, Crabbe fails to describe any problems in consistency between labs demonstrated for the hot plate test as used by Applicants. The hot plate test is a common method to determine sensitivity to pain, and is used by many skilled in the art to test mice, including knockout mice. Furthermore, in the hot plate test described in the instant specification, homozygous knockout mice were compared to wild-type age- and gender-matched wild-type mice in a controlled laboratory setting. The results would be accepted by the skilled artisan as demonstrating a phenotype for the claimed mice, and a role for the TPR6 gene in pain or pain sensitivity. As such, Applicants submit that the Crabbe reference fails to support that the claimed mice lack utility.

The Examiner has cited the Mogil reference (1999, *Pain,* Vol. 80, pages 67-82) as suggesting that inbred mouse strains, having different genetic backgrounds, respond differently to pain. Applicants disagree with these conclusions and believe that this aspect of the rejection does not apply to newly submitted claims 23-27. The Mogil reference relates to a general comparison of nociceptive responses among inbred strains of mice and attempts to determine the effects of genetics/heredity and environment on measures of nociception. The reference does not make any comparisons of phenotypes determined in knockout studies and the effect of strain background on these phenotypes. The specification sufficiently describes production of the claimed mouse exhibiting decreased sensitivity to pain as demonstrated by results in the hot plate test. The transgenic mice were compared, as is standard procedure, to wild-type littermate mice (with a mixed strain background), and determined to have an increased latency to respond to the thermal stimulus as a result of the disruption.

In view the cancellation of claims and arguments set forth above, Applicants believe the rejection of the claims under 35 U.S.C. § 101 is improper, and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6-7, 9, 14 and 16-19 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. Claims 6-7, 9, 14 and 16-19 have been canceled. For the reasons set forth above in response to the utility rejection, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, for lack of utility does not apply to claims 23-27. Therefore, Applicants respectfully request withdrawal of the rejection.

The Examiner has also rejected claims 6-7, 9, 14 and 16-19 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection. Claims 6-7, 9, 14 and 16-19 have been canceled.

The Examiner's enablement rejection relates to the following issues: ES cell technology is limited to the mouse system; the requirement for germline transmission of a genetic disruption to produce a knockout mouse/animal; the unpredictability of a phenotype in a transgenic mouse (or a cell); and the alleged lack of description of a heterozygous mouse or a chimeric mouse, which are allegedly encompassed by the claims. Applicants traverse each aspect of the rejection.

New claims 23-27 address each of the issues raised in the enablement rejection. More particularly, new claims 23-27 overcome the above enablement rejection by: (1) reciting a homozygous disruption of the TRP6 gene in a mouse; (2) reciting the use of embryonic stem cells in the method of producing the mouse; (3) reciting a phenotype described in the specification as a result of the gene disruption; and/or (4) cancellation of the claims.

Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, for enablement is no longer relevant as a result of the cancellation of claims, and request withdrawal of the rejection. Claims 23-27 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-881.

Respectfully submitted,

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Enclosures